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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/445,105	03/07/00	MESSIKA Z	MESSIKA=2

HM22/0829

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EXAMINER	
SEHARASEYON,J	
ART UNIT	**PAPER NUMBER**
1647	8

DATE MAILED: 08/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/445,105	MESSIKA ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to the election and amendment filed on 7/11/01 in Paper No: 6. Applicant's arguments to combine the Groups is persuasive. Thus, Group I and II are combined for examination. Claims 1-6 are pending.

Oath/Declaration

2.The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: The declaration has not been signed by the 3rd inventor. Appropriate correction is required.

Specification

3. The drawing(s) filed on 3/7/00 has been objected to by the draftsperson (see PTO 948). Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claims 1, 2 and 6 are rejected as being vague and indefinite in the recitation of the term "biologically active ". It is unclear what biological activity is encompassed in the instant claims. Therefore, the metes and bounds of the claim are unclear. Claims 3 and 4 are rejected insofar as they depend on claim 2.

4b. Claim 2 is rejected as vague and indefinite for reciting the term "variant", because the term "variant" is not defined in the specification. This is because a variant may encompass a single amino acid change or several amino acid changes and it is unclear what "variants" are encompassed in this claim. Claims 3 and 4 are rejected insofar as they depend on claim 2.

4c. Claim 2 is rejected as being vague and indefinite in the recitation of the term "physiologically active". It is unclear what physiological activity is encompassed in the instant claim. Claims 3 and 4 are rejected insofar as they depend on claim 2.

4d. Claims 5 and 6 are rejected as being vague and indefinite in the recitation of the term "effective amount ". It is unclear what effective amount is encompassed in the instant claim.

Claim Rejections - 35 USC § 112, first paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification describes the art known human tumor necrosis factor (TNF-α) cloning into a vector to produce glycosylated human tumor necrosis factor, meets the

written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose any physiologically active variants. The claims as written, however, encompass nucleotide sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claim 2. Thus, the specification does not provide written support to the genus encompassed by the instant claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116).

With the exception of human TNF-α the skilled artisan cannot envision all the detailed chemical structure of the contemplated nucleotide sequences encompassed, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird,* claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only human TNF-α, but not the full breadth of the claim meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it does not appear that the inventors were in possession of physiologically active

variant sequences set forth in claim 2. Claims 3 and 4 are rejected insofar as they depend on claim 2.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

5b. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human TNF-α, does not reasonably provide enablement for any isolated TNF-α variant nucleic acid molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the

existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The instant claims read on any isolated variant of TNF-α. However, other than TNF-α, which is well known in the art, the specification as filed fails to disclose any other nucleotide sequence which encodes a variant TNF-α protein.

Despite knowledge in the art for producing polypeptides that are variants of a given polypeptide, the specification fails to provide any guidance regarding the changes/differences contemplated and yet retain the function. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. Therefore, predicting which variant of the said molecule will produce physiologically active human TNF-α is well outside the realm of routine experimentation. Thus, undue amount of experimentation would be required to identify sequence of nucleotides encoding variant.
Applicants have not taught how one of skill in the art would use the full scope of sequences encompassed by the invention of claim 2. The specification as filed does not sufficiently teach one of skill in the art how to make and use the full scope of the claimed sequences. The amount of experimentation required to make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the nucleotide sequences, which are differentially expressed. Given the breadth of claim 2, in light of the unpredictability of the art as determined by the lack of

working examples and shown by the prior at of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. Claims 3 and 4 are rejected insofar as they depend on claim 2.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Korn et al. (1988).

The instant invention is directed to glycosylated human tumor necrosis factor protein.

Korn et al. teaches the method for producing biologically active human tumor necrosis factor (TNF-α) protein in Chinese hamster ovary (CHO) cells. There is no difference between the method disclosed in Korn et al. and the one described in the present application in producing the recombinant TNF using CHO cells. Thus, it is assumed that the protein produced by Korn et al. is similarly glycosylated, to the one described in theinstant application. Although, they use CHO cells to produce the protein it does not appear that they recognize that TNF is glycosylated. However, it is well in the art that mammalian cells like CHO cells, provide post-translational modifications to

protein molecules including correct folding or glycosylation at the correct site (Wallach et al.U.S. Patent No: 5,695, 953). Therefore, the disclosure of Korn et al. anticipates claims 1, 2 and 4.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7a. Claims 3,5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korn et al. (1988) in view of Allet et al. in (U.S. Patent No: 5,487,984).

The instant invention is directed to purifying glycosylated human tumor necrosis factor protein, pharmaceutical compositions and methods of treatment.

The relevance of Korn et al. has been set forth above in paragraph 6a. Korn et al. teaches the method for producing biologically active human tumor necrosis factor (TNF-

α) protein in Chinese hamster ovary (CHO) cells. However, they do not describe the purification of the glycosylated TNF. They also do not describe the pharmaceutical composition and the use of the same in treatment of human diseases.

Allet et al. describe the purification of TNF (column 6, lines 61-67), pharmaceutical compositions and treatment of human diseases (column 7, lines 35-43 and column 12, line 4 to column 13, line 5). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods disclosed in Korn et al. to produce and purify the glycosylated TNF protein, obtain pharmaceutical compositions and use it in treating human disease in combination with the teachings of Allet et al. One of ordinary skill would have been motivated with reasonable expectation of success to modify the methods of Korn et al. because Allet et al. teach that recombinant TNF can be purified and formulated into pharmaceutical compositions for treatment of human diseases (column 6, lines 61-67; column 7, lines 35-43 and column 12, line 4 to column 13, line 5). Therefore, the instant invention is *prima facie* obvious over Korn et al. (1988) in view of Allet et al. (U.S. Patent No: 4,879,226).

8. No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS
August 22, 2001

JEFFREY STUCKER
PRIMARY EXAMINER